represent another risk factor for CTEPH (14). The *in situ* thrombosis concept is in line with old studies showing the expression of plasminogen activator inhibitor type 1 in endothelial cells lining CTEPH thrombus channels (1). However, epigenetic modifications of the vWF promotor and increased binding of NFκB2 with enhanced platelet aggregation on endothelial cells represent a novel mechanism of *in situ* thrombosis. We agree with CTEPH basic scientists that *in situ* thrombosis remains an amplifier of pulmonary vascular disease in CTEPH, but the data of Manz and colleagues (5) do not speak against thromboembolism, which appears evident for the CTEPH clinician. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Is There a Role for Using Race-Specific Reference Equations? Yes and No

We know that normal lung function is determined by age, sex, and height, but what is the role of race? Race is considered a socially defined construct and not a biological one (1, 2). One way to assess the contribution of self-reported race or ethnicity to lung function is through statistical modeling. Even though much of the regression error can be accounted for by a variety of anthropomorphic, environmental, nutritional, and socioeconomic factors, small differences in lung function across different racial or ethnic groups remain (3–5), indicating that we need to learn more about the role of race and ethnicity in determining lung function. Another approach is to relate lung function interpreted with and without race-specific equations to important clinical outcomes. This method has suggested that mortality in African Americans is more closely linked to lung function interpreted according to the Third National Health and Nutrition Examination Survey (NHANES-III) White (6) or race nonspecific Global Lung Function Initiative (GLI)-Other (7) reference equations rather than equations specific to African Americans (8–10), questioning the utility of race-specific reference equations.

In this issue of the *Journal*, Baugh and colleagues (pp. 819–829) examine how race influences the association of lung function to chronic obstructive pulmonary disease (COPD) outcomes in African Americans in the SPIROMICS (SubPopulations and InteRmediate Outcome Measures In COPD Study) dataset (11, 12). Lung function

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Originally Published in Press as DOI: 10.1164/rccm.202201-0006ED on February 23, 2022

was interpreted as percent predicted using race-specific equations from NHANES-III applied according to self-identified race or ethnicity, or using the non-Hispanic White equation from NHANES-III (ostensibly to maximize any potential discrepancy) or the GLI-Other equation applied to all participants. A comparison of linear regression modeling error was used to assess if one reference equation was better than another at predicting these outcomes. The key result from this portion of the study was that prediction errors were equivalent or less for nearly all outcomes when FEV_1 was interpreted with the NHANES-III non-Hispanic White or GLI-Other reference equations applied to all rather than using race-specific equations. Similar findings were true for FVC.

The authors also examined which factors contributed to absolute FEV_1 using self-identified race as the primary predictor. The data were analyzed by incorporating multiple covariates that have been shown to adversely affect lung function, including the Area Deprivation Index (ADI), a composite variable designed to incorporate adverse neighborhood exposures (13). In addition, the authors applied a new composite measure designed to capture adverse influences at the individual level, the Adversity–Opportunity Index (AOI). The results showed that African American race or ethnicity was associated with lower FEV_1 relative to the non-Hispanic White race or ethnicity after adjusting for age and height, but the effect was reduced, although still present, after further controlling for multiple factors including the ADI and AOI. Only non-Hispanic White individuals had better lung function with increasing opportunity.

Although the authors acknowledge important limitations in their study, the results highlight that the race-specific reference equations were equivalent at best, and in most cases worse, at predicting important COPD outcomes. Such a finding suggests that race-specific equations are of limited utility and perhaps should be abandoned, at least in the context of this study. The authors explain this result by stating that "race-specific equations may present pathological reductions in lung function as normal, racially specific variation". In other words, for African American patients, race-specific equations reveal higher percent predicted values and can thereby mask important associations of lower lung function with adverse COPD outcomes.

But what else do we learn from this study? First, even after controlling for multiple potential confounding factors, there was still an association between self-identified African American race or ethnicity and lower FEV_1. What explains this association is unclear and calls for further research (14). One possibility, considered by the authors, is that ancestry plays a role. The authors make the important point that interpreting ancestry is complex because "ancestry tracks with … geographic, environmental, and historical factors" not captured by genetic analysis alone (15).

Second, the current study introduced the AOI and highlighted its potential utility in understanding how adversity and opportunity affect lung function. As a novel instrument, the AOI will need to be validated, but the analysis led to the provocative finding that the improvement in lung function with increasing opportunity was true only for non-Hispanic White participants. The authors suggest this may be because of unmeasured racism and include a thoughtful discussion of this possibility along with important historical context.

Third, although the authors succeed in highlighting potential shortcomings of using race-specific equations, they showed that the GLI-Other equation did not perform any better than the NHANES-III non-Hispanic White equation. Because it would seem inappropriate to use the non-Hispanic White equation as a "universal" reference, should we then just use GLI-Other for everyone? As the authors acknowledge, moving toward a universal reference equation has important implications. These include possibly overdiagnosing non-White individuals with disease, especially if lung function is near the lower limit of normal, or disqualifying non-White individuals for lung resection surgery or other therapies, or certain occupations, because their lung function is "too low" relative to predicted values obtained from a race-specific reference equation (16). At the same time, using a race-specific equation may have the unintended consequence of revealing a non-White individual with lung function that is "too high" relative to predicted values obtained from a universal equation, resulting in missed or delayed diagnosis of disease, withholding of treatment, or disqualification for disability, pulmonary rehabilitation, or lung transplant surgery (16). Importantly, race-specific reference equations may "normalize" lower lung function and prevent recognition of factors that may adversely affect lung health (2). In fact, careful consideration of race and ethnicity may improve our insight into important health disparities (1, 17).

How do we reconcile all of this? The article by Baugh and colleagues, together with another article on the same topic by Elmaleh-Sachs and colleagues in the previous issue of the *Journal* (18), demonstrate the limitations and poor performance of using race-specific equations at the population level for predicting COPD outcomes or classifying lower respiratory disease events. The same is true for predicting mortality (8–10). Yet, we still face the problem of how to interpret lung function at the individual level for the patient in whom there is diagnostic uncertainty owing to lung function near the lower limit of normal, or is a candidate for surgery, employment, or disability; such a patient could be misrepresented by either a race-specific or universal reference equation, depending on the situation. When interpretation is concordant between the use of both race-specific and universal reference standards, then the patient's lung function is likely truly normal or abnormal. But when interpretation is discordant, then it will be critically important for the clinician to not rely solely on arbitrary, statistical cutoff values for normal lung function, and instead consider the many factors that contribute to making a clinical diagnosis. A potential solution to defining normal lung function is a precision-medicine approach whereby multiple factors related to lung health, many of which are likely reflected by self-identified race or ethnicity, are incorporated into a reference equation that predicts each individual's optimal lung function (16). However, to provide the best patient care and minimize health disparities, we need to be cautious to not accept that "ethnically normal but globally abnormal" is ideal lung health (19). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Are Bacille Calmette-Guérin Skin Reactions the Most Important Correlates of Bacille Calmette-Guérin's Specific and Nonspecific Effects?

Despite not being a perfect vaccine against tuberculosis (TB), bacille Calmette-Guérin (BCG) has been in use for a century, and the BCG vaccination program remains one of the world's major health achievements with more than 4 billion humans inoculated. Nevertheless, BCG still leaves us with many questions (1). For example, how can it be assessed after vaccination whether long-term protection against TB was induced?

Are measurable proxies of vaccination such as BCG skin reaction characteristics (reaction yes or no, reaction type and size) and the tuberculin skin test (TST) response (yes or no, size) informative to that end?

Surprisingly, for the world's oldest vaccine still in use, this is still debated.

Previous work, with important limitations, did not find an association between BCG scar size and protection against TB (2).

However, studies from when the infant dose of BCG was halved from 0.1 ml to 0.05 ml indicate that the dose of BCG is important for the formation of BCG scars and TST responses (3, 4). Furthermore, many studies, including randomized controlled trials (RCTs), have revealed that vaccination technique and the BCG strain are the main determinants for both developing a skin reaction and the skin reaction size and TST responses (5–7). BCG is difficult to administer intradermally, especially in the thin dermis of a neonate, and adequate vaccination technique increases the likelihood of developing a skin reaction. Regarding strains, BCG-Japan and BCG-Denmark have been better at inducing skin reactions than BCG-Russia. This is in concordance with laboratory studies showing that those strains contain far more mycobacteria with a higher ratio of live versus dead mycobacteria when compared with strains such as BCG-Bulgaria and BCG-Russia (8). Corroborating an association between skin reaction characteristics and TB protection, a large cohort study from Kazakhstan found that BCG-Japan was more efficacious than BCG-Russia in preventing clinical TB notifications and culture-confirmed TB (9).

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Originally Published in Press as DOI: 10.1164/rccm.202112-2863ED on January 31, 2022